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TITLE: Dietary Fat, Fat Metabolizing Genes, and Prostate Cancer Risk in African-Americans and Whites

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Dietary fat has been implicated as a potential promotional factor leading to progression of small, latent, non-metastatic prostate tumors to invasive, metastatic lesions. One possible mechanism is conversion of the n-6 polyunsaturated fatty acids to inflammatory compounds produced by the lipoxygenase (LOX) family of enzymes. We are examining whether genetic variants in the n-6 fatty acid LOX pathways are associated with the risk of prostate cancer in a population-based case control study of advanced prostate cancer among African-Americans and whites in Los Angeles County. In the first year of the study, we finished genotyping three LOX gene polymorphisms, including 12-LOX Gln261Arg, Ser322Asn, and the 5-LOX promoter Sp1 motif polymorphism. In the second year, further genotyping will be performed and the results will be linked to case control status and questionnaire data for association analyses. We will investigate whether genetic variation in specific LOX pathways, in combination with diet, contributes to prostate cancer risk. Our findings could provide a scientific foundation upon which to design dietary intervention trials and may allow us to design strategies for reducing the disparity in prostate cancer burden between African-Americans and other ethnic groups

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**Introduction:**

Other than age, the strongest risk factor for prostate cancer is ethnicity and country of residence. African-Americans have higher mortality from prostate cancer than do other ethnic groups ("Cancer in California 1988-1997", California Cancer Registry, June 2000). It has been suggested that prostate cancer grows at a faster rate and exhibits more aggressive behavior in African-Americans (Powell and Meyskens, 2001). Dietary fat has been implicated as a potential promotional factor leading to progression of small, latent, non-metastatic prostate tumors to invasive, metastatic lesions (Snowden et al, 1984; West et al, 1991; Giovannucci et al, 1993). One mechanism by which fats might promote carcinogenesis is by conversion to eicosaoids, inflammatory compounds produced from n-6 polyunsaturated fatty acids by the lipoxygenase (LOX) family of enzymes (Steele et al, 1999). We hypothesize that dietary n-6 fatty acids, in combination with genetic variants in n-6 fatty acid LOX pathways may influence the development and progression of prostate cancer. Our specific aims are (1) to determine whether LOX genotypes are associated with risk of advanced prostate cancer in African-Americans and whites; (2) to determine whether LOX polymorphisms modify the effect of dietary fat intake on prostate cancer risk. We will test our hypotheses in a population-based case control study of advanced prostate cancer being conducted among African-Americans and whites in Los Angeles County. Using DNA samples for 860 cases (360 African-American and 500 whites) and 520 controls (230 African-American and 290 whites), we will genotype polymorphisms in lipoxygenase (LOX) family genes (5-LOX, 12-LOX and 15-LOXs). Logistic regression will be used to estimate odds ratios and test for effects of genotype and diet-genotype interaction. If we find that genetic variation in specific LOX pathways contributes to prostate cancer risk, this evidence will point to specific components of high fat diets that may increase risk. Such a finding will provide a scientific foundation upon which to design dietary intervention trials and may allow us to design strategies for reducing the disparity in prostate cancer burden between African-Americans and other ethnic groups.

**Body:**

In the approved Statement of Work, we proposed to finish the following work within the first 12 months funding (1 Dec 2003-30 Nov 2004):

a. DNA extraction and quantitation (Month 1-2);
b. Genotype 12-LOX gene Gln261Arg polymorphism (Month 3-6);
c. Genotype 12-LOX gene Ser322Asn polymorphism (Month 7-10);
d. Genotype 5-LOX gene promoter Sp1 motif polymorphism (Month 11-14);

To address task a: So far we have finished DNA extraction and quantitation on total 1317 samples, including 522 African-Americans (381 cases and 141 controls) and 795 whites (501 cases and 294 controls). To reach our goals, we plan to continue to recruit another 90 African-American controls.

To address task b: We have successfully genotyped 12-LOX gene Gln261Arg polymorphism on 1283 DNA samples. The genotype frequencies are 194 Gln/Gln, 576 Gln/Arg, and 513 Arg/Arg. DNA samples that failed for genotyping will be repeated. Further genotyping will also be performed on incoming 90 DNA samples.

To address task c: We have successfully genotyped 12-LOX gene Ser322Asn polymorphism on 1287 DNA samples. The genotype frequencies are 164 Ser/Ser, 510 Ser/Asn, and 613 Asn/Asn. DNA samples that

failed for genotyping will be repeated. Further genotyping will also be performed on incoming 90 DNA samples.

To address task d: We have successfully genotyped the 5-LOX gene Sp1 motif polymorphism on 1193 DNA samples. The genotypes are summarized in the following table. There are 97 DNA samples remaining that need to be genotyped. 27 DNA samples failed for genotyping and will be repeated. Further genotyping will also be performed on incoming 90 DNA samples.

| 5-LOX Genotype | Number |
|---|---|
| 5/5 (wild type) | 596 |
| 4/5 | 284 |
| 3/5 | 144 |
| 5/6 | 29 |
| 3/3 | 43 |
| 3/4 | 40 |
| 4/4 | 28 |
| 5/7 | 10 |
| 3/6 | 10 |
| 4/6 | 17 |
| 4/7 | 1 |
| 3/7 | 1 |

In addition, we also finished part of the genotyping of the 5-LOX gene Lys254Glu polymorphism and 15-LOX-2 gene Gln656Arg polymorphism, which were planned in the Statement of Work to be done in the second year.

**Key Research Accomplishments**

Successfully extracted and quantitated 1317 DNA samples;
Successfully genotyped the 12-LOX gene Gln261Arg polymorphism on 1283 DNA samples;
Successfully genotyped the 12-LOX gene Ser322Asn polymorphism on 1287 DNA samples;
Successfully genotyped the 5-LOX gene promoter Sp1 motif polymorphism on 1193 DNA samples.

**Reportable Outcomes:**

None

**Conclusions:**

None

**References**

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**Appendices**

None